REMARKS

I. Support for the Amendments to the Claims

Claims 1-13 and 29-53 are currently in the application. Claim 1 has been amended and new claims 29-53 have been added to the present application. Claims 14-28 were previously withdrawn.

Support for the amendments to claim 1 and for new claims 29-53 can be found in the original specification, Examples, Figures, and claims. Additional support for new claims 29-53 can be found in the language of original claims 1-13 and from page 5, line 23, to page 10, line 11; in the Examples; and in the Figures. Additional support for the amendments to claim 1 and for new claims 29-53 can be found, e.g., from page 5, line 23, to page 8, line 6; from page 8, line 27, to page 9, line 25; in Example 1; and in the Figures, especially Figures 3-5.

II. Status of the Claims

Claims 1-28 were previously in the application. The claims were subject to an Election/Restriction Requirement, and claims 1-13 (Group I) were elected with traverse.

Claims 1-13 and 29-53 are currently in the application. Claim 1 has been amended and new claims 29-53 have been added to the present application. Claims 14-28 are withdrawn.

III. The Priority Claim

The present application is a 35 U.S.C. §371 national stage of PCT application PCT/US2004/021637, filed July 6, 2004, which claims the priority benefit of U.S. Provisional

Application Serial No. 60/485,509, filed July 6, 2003, and U.S. Provisional Application Serial No. 60/485,607, filed July 7, 2003, the disclosures of all of which are incorporated herein by reference. Applicants respectfully request acknowledgement of the priority claim.

IV. The Drawings

Applicants respectfully request consideration and acceptance of the drawings.

V. The Information Disclosure Statements

Applicants thank the Examiner for acknowledging the Information Disclosure Statements of February 24, 2006 and January 17, 2007. Applicants respectfully request consideration of the Information Disclosure Statement and references submitted herewith.

VI. The Restriction Requirement

Applicants respectfully request the Examiner to consider whether any rejoinder of claims (e.g., Group IV [claim 25]) is possible at this stage in the prosecution should the remaining claims prove allowable. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call Applicants' undersigned representative as soon as convenient.

VII. The Rejection of Claims 1-4, 7-9, 12, and 13 Under 35 U.S.C. §102(b) over Hagihara is Traversed

The Examiner has rejected claims 1-4, 7-9, 12, and 13 under 35 U.S.C. §102 for alleged anticipation by Hagihara et al. (J. Immunol. Methods 253: 45-55 [2001]). Applicants traverse the rejection and respectfully request reconsideration of these claims.

The Patent Office alleges in pertinent part:

> Hagihara et al. disclose a method for the production of differentiated hematopoietic cells including dendritic cells wherein the method comprises 1) step of culturing CD34+ bone marrow stem cells in the presence of steel factor, thrombopoietin and FLT-3 ligand or under conditions that promote synchronous progression through the cell; 2) subsequent step of contacting the cells with growth factor GM-CSF at a predetermined time and 3) subculturing the cells with a growth factor GM-CSF for up to 14 days or about 14 days. (entire document including abstract and page 49 at section 2.4 "Culture system"). The method taught by Hagihara et al. comprises identical active steps and it results in the production of the differentiated hematopoietic cells as required by the claimed method and, thus, the cited reference by Hagihara et al. clearly anticipates claimed invention of the instant claims 1-4 and 13. Although production or generation of dendritic cells is a primary goal of the cited reference by Hagihara et al., the dendritic cells were not the sole cellular product of the disclosed culturing method and, thus, the final subculture after subculturing with maturation factors including GM-CSF and/or steel factor is reasonably expected to "comprise" at least some amounts of megakaryocytes, granulocytes and platelets within the broadest reasonable meaning of the claims 7-9 and 12. [Pp. 3-4.]

Applicants respectfully disagree.

For example, elsewhere in the Office Action, the Patent Office acknowledges:

> The cited reference by Hagihara et al does not clearly recognize that the cell culturing in the presence of steel factor (SCF), thrombopoietin (TPO) and FLT-3 ligand (FLT3) promotes synchronous progression of cells through the cell cycle. [P. 5.]

Not only does Hagihara fail to disclose synchronous progression of cells through the cell cycle, Hagihara also does not disclose contacting synchronously cycling cells with a growth factor or cytokine "at a predetermined phase of the cell cycle."

Instead, the cells in Hagihara were subsequently subcultured "every week" with no disclosure regarding the timing of the subculturing with regard to the cell cycle. Hagihara does not even disclose whether the subculturing of the cells took place at the same time of day on the same day of "every week." (Applicants also wish to note respectfully that CD34+ cells are not necessarily stem cells.)

Applicants respectfully submit, therefore, that it cannot be concluded by one of ordinary skill in the art that synchronously cycled cell cultures were subcultured with a growth factor or cytokine "at a predetermined phase of the cell cycle."

Claims 2-4, 7-9, and 12-13 are directly or indirectly dependent on claim 1 as an underlying claim, and the arguments and limitations of claim 1 apply to claims 2-4, 7-9, and 12-13 as well.

Applicants respectfully submit that remaining claims 1-4, 7-9, and 12-13 fulfill the requirements of 35 U.S.C. §102(b), thereby placing these claims in condition for allowance, and request the Examiner's reconsideration accordingly.

VIII. The Rejection of Claims 1-13 under 35 U.S.C. §103(a) over Hagihara Taken with Yan, Klabusay, Ramsfjell, and Messner is Traversed, but Rendered Moot in Part

The Examiner has rejected claims 1-13 under 35 U.S.C. 103(a) as unpatentable over Hagihara et al. (J. Immunol. Methods 253: 45-55 [2001]) in view of Yan et al. (Blood, 96(11; part 1): 680a (November 2000) ("Yan")); Klabusay et al. (Blood 100(11): 4118 (November 2002) ("Klabusay")); Ramsfjell et al. (Blood 88(12): 4481-4492 (December 1996) ("Ramsfjell")); and Messner et al. (Blood 70(5): 1425-1432 (November 1987) ("Messner")). Applicants traverse the rejection and respectfully request reconsideration of these claims.

The Patent Office alleges in pertinent part:

> The cited reference by Hagihara et al does not clearly recognize that the cell culturing in the presence of steel factor (SCF), thrombopoietin (TPO) and FLT-3 ligand (FLT3) promotes synchronous progression of cells through the cell cycle. But the reference by Yan et al. provides for the teaching that combination of SCF, TPO and FLT-3 stimulates hematopoietic bone marrow cells to enter into synchronous cell cycle (abstract).
>
> The cited reference by Hagihara et al. is lacking particular disclosure about the use of G-CSF for generating differentiated hematopoietic cells. However, the reference by Klabusay et al. teaches that hematopoietic stem cells are able to regenerate hematopoiesis in all lineages and that addition of G-SSF in particular will significantly increase the number of maturated cells including granulocytes (see abstract). The reference by Ramsfjell et al. teaches that the use of factor SCF enhances megakaryocyte differentiation and production from stem cells.
>
> Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify method of Hagihara et al. by adding G-CSF and steel factor (SCF) during subsequent culturing/subculturing steps with a reasonable expectation of success in producing differentiated hematopoietic cells including megakaryocytes and granulocytes because the prior art teaches and suggests the use of G-CSF and SCF for enhancing production of granulocytes and megakaryocytes. It is well known that platelets are products of megakaryocytes. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.
>
> Further, the reference by Messner et al. teaches that cell cycle studies and stem cell engraftment studies indicate that the higher than normal proportions of multipotential hematopoietic cells are present in S phase during progression of the hematopoietic cells through the cell cycles (see abstract). Thus, one of skill in the art would have been motivated to contact the hematopoietic stem cells with maturation factors at the time of cell progression through S phase for the expected benefits in maximizing yields of matured differentiated hematopoietic cells derived from the stem cells. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. [Pp. 5-6.]

Applicants respectfully disagree, in part for reasons already discussed above with respect to Hagihara, namely, that not only does Hagihara fail to disclose or suggest synchronous progression of cells through the cell cycle, Hagihara also does not disclose or suggest contacting synchronously cycling cells with a growth factor or cytokine "at a predetermined phase of the cell cycle."

Yan, Klabusay, Ramsfjell, and Messner, taken either alone or in combination together, fail to supply the deficiencies of Hagihara.

With respect to Yan, the Yan culture was quiescent (97.4% G0/G1 phase; 1.5% S phase), but was stimulated by cytokines to enter into cycle as early as 24 hours to yield a fast-dividing population and a slow-dividing population, whereas the cells of the present invention are cultured from dormancy to synchronous cycles and then stimulated by exposure "at a predetermined phase of the cell cycle."

With respect to Klabusay and Ramsfjell, Applicants respectfully submit that while these references may disclose the generation of various hematopoietic lineages, neither of these references, either alone or in combination with each other or with Hagihara and/or Yan, discloses nor suggests from a synchronous population of stem cells by exposure "at a predetermined phase of the cell cycle."

With respect to Messner, this work is irrelevant to the present invention, as it found variations in frequencies of clonogenic precursors in the normal donor population, but also included marrow from leukemic patients, which cannot be equated with normal marrow. The cell cycle was addressed primarily to determinte the proportion of clonogenic precursors in S-phase by preincubation with tritiated thymidine, rather than synchronizing the cell cycles or by exposure of a synchronous population of stem cells "at a predetermined phase of the cell cycle."

Nor would one of ordinary skill in the art be motivated to combine Hagihara, Yan, Klabusay, Ramsfjell, and Messner to arrive at the present invention. The present invention is not a combination, simple substitution, or improvement of known elements or methods to yield a predictable result. One of ordinary skill in the art would not have considered it "obvious to try" with any reasonable expectation of success.

None of these references describes or suggests the selection of "a predetermined phase of the cell cycle" or differentiation "hotspot" as a method for selecting a specific differentiation pathway to yield cell cycle specific differentiated hematopoietic cells. None of these references describes or suggests the reversibility of the "predetermined phase of the cell cycle" or differentiation "hotspot" (see Example 1 and Figures 3-5).

Thus, the unpredictability of the present invention goes far beyond a combination, simple substitution, or improvement of known elements or methods and would not have been "obvious to try."

Applicants note that claim 1 is an underlying claim for claims 2-13 and that the arguments that apply to claim 1 also apply to these claims.

Applicants respectfully submit that claims 1-13 fulfill the requirements of 35 U.S.C. §103(a), thereby placing these claims in condition for allowance, and request the Examiner's reconsideration accordingly.

CONCLUSION

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

Applicants respectfully request a three-month extension of time for the Amendment and accompanying materials and submit the appropriate fee herewith. If, however, a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time and the Commissioner is hereby authorized to charge our deposit account no. 04-1105 for the appropriate fee. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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Kathryn A. Piffat, Ph.D. (Reg. No. 34,901)
Intellectual Property Practice Group
EDWARDS ANGELL PALMER & DODGE, LLP
P.O. Box 55874
Boston, Massachusetts 02205
Telephone: 617-239-0100

Customer No. 21874